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CONTRACTING ORGANIZATION:
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14. ABSTRACT
The purpose of this project is to identify the incidence of post traumatic hypopituitarism (PTH) in mild TBI and develop criteria for assessing which patients with a mild TBI are at risk for developing PTH. This study will also correlate the characteristics of the individuals with PTH by neuropsychological, neurophysiological and imaging testing as they relate to functional outcome. At 6 months post injury, patients will be screened for anterior pituitary function f the 61 mTBI subjects with IGF-1 results at the 6 month visit, the results fell below the lower threshold for 13.1% when using the Quest Diagnostics reference values. However, when the TBI threshold was used, there were 31 subjects (50.8%) that met the criteria for hypopituitarism, with this finding, similar to that found in moderate-severe TBI population.

15. SUBJECT TERMS
Post traumatic hypopituitarism

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Introduction

This report outlines Dr. Masel's participation in the Mission Connect Mild Traumatic Brain Injury (mTBI) Translational Research Consortium during the time period of August 1, 2013 through August 1, 2014. Dr. Masel is the PI for Specific Aim 2.3, which is designed to study the diagnosis of post traumatic hypopituitarism after mTBI. The research activities of Specific Aim 2.3 are being conducted in collaboration with three other clinical projects in the Consortium: Specific Aims 2.1 (PI Levin), 2.2 (PI Papanicalaou/McCarthy), and 3.1.2-3.1.7 (PI Robertson) as the Integrated Clinical Protocol (ICP), which will use a shared group of subjects. This project uses only the mTBI subjects, for whom we determine the incidence of hypopituitarism following mTBI and develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening. We also determine the relationship between post-traumatic hypopituitarism and functional outcome, cognitive recovery, and resolution of PCS at six months after mTBI. We will also examine the incidence of single and multiple pituitary hormone deficiencies. The clinical characteristics, MRI imaging results, EEG and MEG results of the subjects who have pituitary deficiency will be compared to those with normal pituitary function. The relationship between pituitary dysfunction and functional outcome, cognitive recovery, and resolution of PCS will be examined.

Body of report

SA #2.3: To study diagnosis of post-traumatic hypopituitarism after mTBI
SA #2.3.1: To determine the incidence of hypopituitarism following mTBI.
SA #2.3.2: To develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening.

At the 6 Month Visit, mTBI subjects have blood samples drawn to examine six hormone levels that are indicative of anterior pituitary function, including somatomedin (IGF-1), thyroid stimulating hormone (TSH), thyroxine (Free T4), prolactin, and total cortisol in all subjects. Total testosterone is tested in male subjects, and 17 β-estradiols is tested in females.

As of August 1, 2014, 71 subjects completed the 6 month visit when pituitary labs are done; of these 61 had IGF-1 levels available for analysis. (See Table 1 below) To our knowledge, there is no ongoing study of this type (looking for pituitary dysfunction in mTBI), size or scope in the United States. Please see the Conclusion section for more detail. For a full discussion of subject screening and recruitment, please refer to Dr. Levin's report.

A summary of the mean, standard deviation, and ranges of the test results of pituitary function are presented in Table 1 below. The number of subjects falling outside the standard reference range results is also presented.

Table 1: Summary of Pituitary Test Results

Cortisol						Out of Range			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	10.1	4.4	3.4	21.8	0		0	
Male	44	10.8	4.4	2.4	20.0	1	2%	0	
All	66	10.6	4.4	2.4	21.8	1	1%	0	
Estradiols						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	21	75.0	56.6	11.8	207.4	1	5%	1	5%
IGF-1/Somatomedin						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	21	167.9	64.3	62.0	267.0	refer to IGF-1 Table			
Male	40	182.8	76.9	65.0	388.0				
All	61	177.6	72.6	62.0	388.0				
Prolactin						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	10.9	9.8	4.5	47.8	0		2	5%
Male	45	9.3	4.9	3.2	25.5	0		2	5%
All	67	9.8	6.8	3.2	47.8	0		4	5%
TSH						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	1.5	1.6	0.3	8.0	1	5%	1	5%
Male	46	1.6	1.2	0.5	6.2	0		3	7%
All	68	1.6	1.3	0.3	8.0	1	1%	4	6%
Thyroxine (Free T4)						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	1.0	0.1	0.8	1.3	0		0	
Male	46	1.0	0.1	0.8	1.3	1		0	
All	68	1.0	0.1	0.8	1.3	1		0	
Total Testosterone						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Male	42	394.0	187.1	106.0	819.0	10	24%	0	

A separate table for the out-of-range values for IGF-1 is provided (Table 2 below), since these results are gender and age dependent. Table 2 indicates two parameters used to determine IGF-1 deficiency. The first (labeled: Standard Values) are the age/gender specific values used by Quest Diagnostics, the outside lab that does the IGF-1 test for Memorial Hermann Hospital-Texas Medical Center. However, IGF-I is a very rough estimate of the GH status of an individual and GH provocative stimulation testing, such as with the glucagon stimulation test (GST) is the only way to make a definitive diagnosis of growth hormone deficiency. The normal ranges for IGF-I are difficult to interpret, especially in individuals with TBIs because IGF-I can be influenced by many different variables. Therefore, there are GH deficient subjects who will have IGF-I levels in the normal range. The cutoff of an IGF-I of less than 175 (labeled TBI Values) is based on our study that correlated the response of the GST with the baseline IGF-I. (Zgaljardic et al., 2011). Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing.

Table 2: Subjects with Low IGF-1/Somatomedin Values

Standard* Reference Values				Standard Values		TBI Values**	
Age	**Female (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	128-488 ng/mL	9	1	2	22%	2	22%
25-29 years	89-397 ng/mL	3		0		2	67%
30-34 years	71-352 ng/mL	1		0		0	
35-39 years	63-330 ng/mL	0	1	0		0	
40-44 years	58-318 ng/mL	5		1	20%	5	100%
45-49 years	54-307 ng/mL	2		0		2	100%
		20	2	3	15%	11	55%
Standard* Reference Values				**Standard Values**		**TBI Values****	
Age	**Male (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	121-423 ng/mL	19	2	1		4	21%
25-29 years	112-402 ng/mL	6	1	2	33%	3	50%
30-34 years	89-350 ng/mL	5	2	1	20%	5	100%
35-39 years	77-323 ng/mL	4	2	0		3	75%
40-44 years	70-307 ng/mL	5	0	0		4	80%
45-49 years	66-296 ng/mL	2	1	1		4	100%
		41	9	5	12%	21	51%
*reference lab values **TBI values (Zgaljardic et al., 2011)							

The missing IGF-1 results shown in Table 2 are due to:

1. Incorrect IGF test entered by lab personnel (5)
2. Lab tests not done after sample was drawn (1)
3. Lab tests done but result cannot be located (4)

The lab order sheet for the 6 Month Visit has been revised to increase the accuracy of test entry by the lab personnel, and we are monitoring this very closely. The Research Team meets regularly with the CRU staff to ensure that they are familiar with all aspects of the protocol, and we have increased this interaction as well. To put this in perspective, the mTBI subjects get 6 lab tests for pituitary function at the 6 Month Visit. For the 71 enrolled mTBIs that have completed the 6 Month Visit, this would be a total of 426 tests. The errors in this group represent 2.34% of the tests done.

Key research accomplishments

- Dr. Masel has been an active participant in the Clinical Working Group as well as at the Partnering PI Quarterly meetings.

- Dr. Masel was an author on the following paper addressing the topic of post traumatic hypopituitarism as it relates to fatigue in the past year: Zgalijardic, D. J., Durham, W. J., Mossberg, K. A., Foreman, J., Joshipura, K., Masel, B. E., Sheffield-Moore, M. (2014). Neuropsychological and physiological correlates of fatigue following traumatic brain injury. Brain Injury, 28(4), 389-397.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Mission Connect Consortium Retreat, January 13, 2014, Galveston, Texas.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Arkansas Trauma Conference, Little Rock, Arkansas, May 22, 2014.

- Dr. Masel co-authored the following book chapter with a section on post traumatic hypopituitarism in the past year: Masel, B. E., & DeWitt, D. S. (2014). Traumatic brain injury disease: Long- term consequences of traumatic brain injury. In Understanding traumatic brain injury (pp. 28-53). New York NY: Oxford University Press.

Reportable outcomes

1. The analysis of pituitary hormones showed that of the subjects tested using the conservative testing values, 3 females (15%) and 5 males (15%) had low IGF-1 values indicative of Growth Hormone Deficiency. Using research-defined" TBI values (see reference above) 11 females (55%) and 20 males (56%) had low values for IGF-1.

2. IGF-1 deficiency was the most common finding

3. Testosterone deficiency was the second most common finding

4. Similar to moderate-severe TBIs, pituitary deficiencies are surprisingly common at six months following mild TBI.

Conclusion

By the end of Year 6, enough mTBI subjects have completed their 6 month visit to provide very good preliminary data for analysis. We have found that post traumatic hypopituitarism is prevalent at the 6 month time point following a mTBI. A low IGF-1 (an indicator of low growth hormone levels) is the most common hormonal deficiency, with testosterone the next most common deficiency. Interestingly, these findings are surprisingly consistent with the moderate-severe TBI hypopituitarism literature, where GH deficiencies are present in approximately 15-20% of those studied, and testosterone deficiency is approximately 5-10%. Of note, the moderate-severe TBI literature is mostly one year or more post injury, and we do not know if there would be some pituitary recovery in the population we are studying by month twelve.

We previously had run a very preliminary analysis of our data with the neuropsychological findings by Dr. Levin, and found a small relationship of pituitary dysfunction to acute symptoms as well as depressive measures. In the next quarter, we will be able to run a final analysis, and will identify what deficits and symptoms are specific to those with pituitary deficiencies. We anticipate producing one or more scientific publications on our results. Obviously, we will also work with other Consortium scientists to see if there is any commonality of hypopituitarism to EEG and/or imaging studies. Should there be positive findings, separate scientific publications will be produced.

It's obviously important to identify abnormalities. The more important question will be whether or not treatment of the abnormalities can change symptoms. Based upon the data obtained from

SA 2.3 and ***2.3.1***, we have obtained private funding, medications and placebo, as well as local IRB approval, and have begun recruitment for a pilot study of subjects with mild TBIs who complain of fatigue. (Upon final approval from the Baylor and UT Houston IRBs, subjects who have participated in the Mission Connect Consortium study will be contacted as well.) Subjects will be re-screened for pituitary dysfunction. Those who have Growth Hormone deficiencies and complain of fatigue will be evaluated and treated. Note that the data on GH deficiencies in the Mission Connect Consortium study is based on a "screening" level (IGF-1). This new study will re-screen these individuals at least one year post injury and perform definitive (provocative) testing for GH deficiencies.

It is a well-accepted concept that post traumatic hypopituitarism following a moderate-severe TBI is fluid in the first year post injury. Some deficiencies resolve; some develop later. It is believed that around one year, however, the deficits become permanent. We have no such knowledge relative to mild TBI. By re-screening (and treating) the subjects enrolled in the Mission Connect Consortium study who are now more than one year post injury, we will see what deficiencies resolve and what new deficiencies develop and are now considered permanent. This will more definitively respond to ***SA #2.3.1:*** "To determine the incidence of hypopituitarism following mTBI."

As we will know what deficiencies are permanent at one year, using our data from our 6 month screening, we will also be able more definitively achieve the goals set out in ***SA #2.3.2:*** "To develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening." For example, we may be able to identify 6 month cut-offs for deficiencies that separate those whose deficiencies resolve from those who become or continue to be deficient, thus, obviating the need for further study of that group. Considering the very large number of mild TBIs, we anticipate that these results will be of great interest to the civilian and the military population.

Reference

Zgaljardic, et al. (2011) Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing, *Clinical Endocrinology* 74, 365–369

Appendices—Quad Chart

Post-traumatic Hypopituitarism after Mild TBI

W81XWH-08-2-0138 PT074693P7

PI: Brent E. Masel, MD **Org: Transitional Learning Center at Galveston** **Award Amount**: $125,000

Study Aims

- Determine incidence of hypopituitarism after mTBI
- Identify risk factors in mTBI patients for this condition
- Describe relationship between post-traumatic hypopituitarism and functional outcome, cognitive recovery, and resolution of PCS

Approach

The goal of our research consortium is to improve the diagnosis and treatment of mTBI. The Integrated Clinical Protocol has 4 related studies conducted in a sample of 200 mTBI subjects and 100 subjects with orthopedic injuries, as a comparison group; however, only mTBi subjects will participate in this study.

Specific Aim 2.3 is designed to examine the incidence and effects of hypopituitarism after mTBI, which are currently unknown. In this study, the clinical characteristics, MRI imaging results, EEG and MEG results of the patients who have pituitary deficiency will be compared to those of patients with normal pituitary function. The relationship between pituitary dysfunction and functional outcome, cognitive recovery, and resolution of PCS will be examined.

Standard* Reference Values				Standard Values		TBI Values**	
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30-34 years	71-352 ng/mL	1		0		0	
35-39 years	63-330 ng/mL	0	1				
40-44 years	58-318 ng/mL	5		0		5	100%
45-49 years	54-307 ng/mL	2		0		2	100%
		20	2	2	10%	11	55%

Standard* Reference Values				Standard Values		TBI Values**	
Age	Male (ng/ml)	n	missing	Low	%	Low	%
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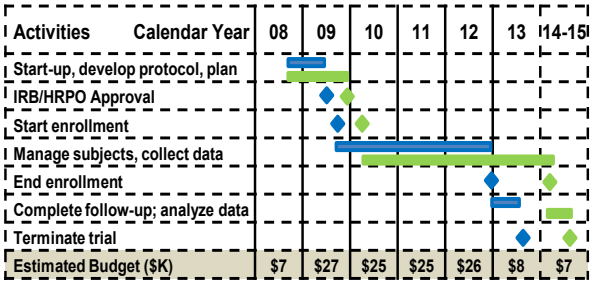
30-34 years	89-350 ng/mL	5	2	1	20%	5	100%
35-39 years	77-323 ng/mL	4	2	0		3	75%
40-44 years	70-307 ng/mL	5	0	0		4	80%
45-49 years	66-296 ng/mL	2	1	1		2	100%
		41	9	5	12%	21	51%

Accomplishment: We learned that individuals with mTBI have an unexpectedly high incidence of growth hormone and testosterone deficiencies, similar to more severe TBIs. Due to these findings, we have obtained outside funding to now do a treatment trial.

Timeline and Cost

Original Funding Period – Aug 1, 2008 – July 31, 2013
Extension Years Funding – Aug 1, 2013 – July 31, 2015
Key: blue – planned, green -- actual



Updated: August, 2014

Goals/Milestones

CY08-09 Goals – Kick-off project, develop protocol, operational planning
☑ Initial draft of Integrated Clinical Protocol, Fall 2009
☑ Approvals from both IRBs and recruitment sites in Summer 2009
☑ HRPO approval December 2009

CY10-11 Goals – Start enrollment, manage subjects, collect data
☑ Enrollment begun February 2010
☑ Transition from paper CRFs to electronic data entry, January 2011

CY12-13 Goal – Increase enrollment, collect high-quality data
☑ 33 subjects' pituitary lab results analyzed and included in February 2012 Quarterly Report
☑ **CY 13-14 Goal** – Increase enrollment
CY 14-15 Goal – Complete study and analyze results

Comments/Challenges/Issues/Concerns

- Sample drawn at 6 Month Visit, so subject attrition is a concern
- 82% of subjects completing all study activities, with 68 mTBI subjects completing this study and 61 with IGF-1 results

Budget Expenditure to Date

Projected Expenditure: $125,000—Actual Expenditure: $125,000